Available online at www.ijpcr.com
International Journal of Pharmaceutical and Clinical Research 2017; 9(5): 343-352
doi: 10.25258/ijpcr.v9i5.8594

ISSN- 0975 1556

Research Article

A Study of Sleep Disorders in Patients with Chronic Kidney Disease (CKD)

Hussein A[1*], El-Hadidy A[1], Gomaa N, Amin Y[1], El-Shabouny T[1]

[1]*Pulmonary Medicine, Faculty of Medicine, Cairo University, Egypt*
[2]*Department of Pulmonary Medicine, National Research Center*

Available Online: 25th May, 2017

ABSTRACT

Sleep apnea is an important comorbidity in patients with chronic kidney disease (CKD). Although the increased prevalence of sleep apnea in patients with CKD is well established, few studies have examined the full spectrum of kidney function. We sought to determine the prevalence of sleep apnea and associated nocturnal hypoxia in patients with CKD. We hypothesized that the prevalence of sleep apnea would increase progressively as kidney function declines. 45 patients were recruited from outpatient nephrology clinics, nephrology department, and hemodialysis units. All patients completed an overnight inpatient polysomnograhy test to determine the prevalence of sleep apnea (AHI ≥ 5 events /h) and nocturnal hypoxia (oxygen saturation (SaO2) below 90% for ≥12% of the nocturnal monitoring time). Patients were stratified according to their estimated glomerular filtration rate (eGFR) at the time of the study visit into three groups as follows: CKD stage 2 (eGFR 60 to 89 mL/min/1.73 m2) (control group), CKD stages 3 and 4 (eGFR 15 to 59 mL/min/1.73 m2), and CKD stage 5 (eGFR <15 mL/min/1.73 m2). eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Out of the 45 patients included in our study with the full spectrum of kidney function, ranging from those with eGFR 60 to 89 ml/min./1.73m2 to patients with eGFR <15 ml/min./1.73m2, 15 (33.3%) had sleep apnea (Mean AHI; 8.71±5.86). Our study found that prevalence of sleep apnea increased as kidney function declined (Group (I), 20%; Group (II), 36.4%; Group (III), 37.5%). Furthermore, severity of sleep apnea increased as kidney function declined (Group (I), mean AHI: 5.75±0.35; Group (II), mean AHI: 6±1.38; Group (III), mean AHI: 10.6±7.04). We also found that prevalence of nocturnal hypoxia which is characteristically associated with sleep apnea was greater among groups (II) and (III) (27.3% and 16.7%, respectively) than in group (I) (10%). Severity of nocturnal hypoxia increased as kidney function declined (Group (I), 13%; Group (II), 13.6±1.22%; Group (III), 16.75±3.30%). Overall, 8 out of the 45 studied CKD patients (17.8%) had nocturnal hypoxia (Mean SaO2 below 90% for ≥12% of the nocturnal monitoring time; 15.1±2.87%). Our study revealed that as kidney function declined, Apnea/Hypopnea (AHI) indices increased, oxygen desaturation indices increased, minimal peripheral capillary oxygen saturation values decreased, peripheral capillary oxygen saturation time <90% increased, and snore indices increased. Also, respiratory distress index (RDI) was higher among groups (II) and (III) than in group (I). However, only differences between groups as regards respiratory distress events, respiratory distress indices, snore events, and snore indices were statistically significant. These results show that as kidney function declines, several respiratory parameters deteriorate during sleep. In addition, wake events and indices, and sleep stage 1 (%) increased as kidney function deteriorated. Sleep efficiency (%) was highest among group (I) patients and lower among groups (II) and (III), Light sleep (%) was lowest among group (I) patients and higher among groups (II) and (III), and deep sleep (%) was highest among group (I) patients and lower among groups (II) and (III). It is clear from the above results that as kidney function declines, sleep efficiency deteriorates, wake indices increase, light sleep (%) increases, and deep sleep (%) decreases. We concluded that prevalence and severity of sleep apnea in patients with CKD increase as kidney function declines. Almost 18% of patients with CKD experience nocturnal hypoxia, which may contribute to loss of kidney function.

Keywords:

INTRODUCTION

Sleep apnea (SA) is defined as an intermittent interruption of airflow at the level of nose and mouth during sleep. Episodes of apnea are considered important if they persist for longer than 10 seconds, but in some cases they may last as long as 2 minutes. The SA syndrome is the clinical consequence of frequent episodes of apnea during sleep. Usually patients with the full-blown syndrome have at least ten episodes of apnea per hour. The syndrome is probably the most important cause of daytime somnolence[1].

Sleep apnea (SA) may be obstructive or central. Obstructive sleep apnea (OSA) is characterized by a complete or partial obstruction of the upper airways, due to relaxation of the musculature combined with mechanical factors, such as tissue adiposity and cranio-facial structure, which causes apnoea or hypopnoea during sleep[2]. Central apnoea (CSA) on the other hand is due to a cessation of voluntary respiratory drive from the central respiratory centre in the hypothalamus[3]. The airway remains open during CSAs/hypopnoeas. These apnoeas and hypopnoeas are often accompanied by arterial hypoxia, a rise

**Author for Correspondence: aliiihussein@gmail.com*

Figure 1: Parts of SOMNO screen TM plus polysomnography.

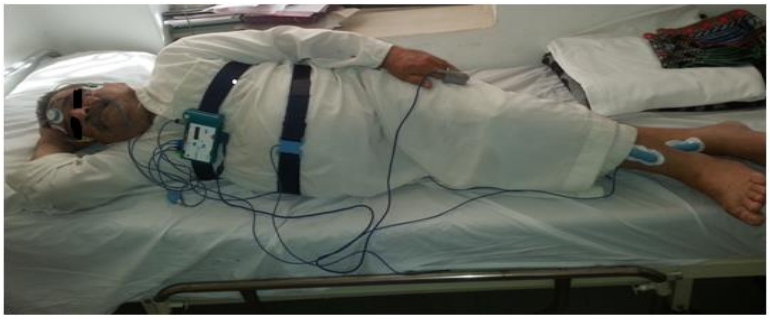

Figure 2: During PSG, the patient sleeps while connected to a variety of monitoring devices.

in carbon dioxide and increased sympathomimetic discharge. The net result is a repetitive interruption of nocturnal sleep, increased heart rate, reversal of the diurnal variation of blood pressure and daytime fatigue and hypersomnolence. There are complex relationships between SA and increased cardiovascular risks. Patients are at increased risk of developing essential hypertension, heart disease and mortality due to cardiovascular causes[4]. There is an increased risk of ischaemic stroke in patients with untreated SA and direct consequences on recent memory retention, reduced neuro-psychological function, depression and deteriorating quality of life[5].

The coexistence of sleep apnea in patients with Chronic Kidney Disease (CKD) and End-Stage Renal Disease (ESRD) is likely to have clinical relevance. In addition to impairment of sleep quality and daytime function[6], sleep apnea increases the risk of hypertension[7], atherosclerosis, and vascular disease[8]. Vascular disorders are common to both patients with CKD and patients with ESRD, and their prevalence may be further increased by unrecognized sleep apnea[9]. Further, sleep apnea is characteristically associated with nocturnal hypoxia, which is the main biologic mechanism through which these vascular complications develop[9]. It is also possible that sleep apnea accelerates the deterioration of kidney function in patients with CKD either indirectly by increasing systemic BP, inflammatory cytokines, and sympathetic nervous system activity[10] (all of which have been proposed to reduce kidney function) or directly through the effect of hypoxia on the kidney[11].

There are several reasons why the increased risk of OSA is significantly associated with decreased glomerular filtration rate (GFR) among these patients. First, the upper airway dimensions in patients with renal failure are prone to narrowing. Beecroft et al. reported that the pharyngeal cross-sectional area measured by pharyngometry in end-stage renal disease patients was 12% less than that in the normal renal function control group matched for body mass index (BMI)[12]. Such pharyngeal narrowing was considered to occur because of upper airway edema due to systemic fluid overload and upper airway dilator muscle dysfunction due to neuropathy or myopathy associated with chronic uremia[12]. Second, ventilation control is known to be instable in CKD patients. Because chemoreflex responsiveness has been reported to be augmented in patients with end-stage renal disease, possibly because of the accumulation of uremic molecules or metabolic acidosis, this destabilized respiratory control—as explained by a high "loop gain" theory—can contribute to the pathogenesis of OSA[13]. Although these two mechanisms have been established in hemodialysis patients, it is possible that they are also applicable to the nondialysis CKD population.

Nocturnal hypoxia has been demonstrated to be independently

associated with an increased risk for accelerated loss of kidney function[14]. The chronic hypoxia hypothesis suggests that chronic ischemic damage in the tubulointerstitium of the kidney is the final common pathway for the development of ESRD[11]. If such a process is already under way in patients with CKD, it is possible that ongoing nocturnal hypoxia will amplify the effect and accelerate the decline in kidney function. If so, identification and treatment of nocturnal hypoxia may provide a potential disease-modifying intervention that could delay or halt the progression of CKD to ESRD.

Aim of work

The aim of this work is to study sleep-disordered breathing in patients with chronic kidney disease.

SUBJECTS AND METHODS

Among adult patients attending outpatient nephrology clinics, hemodialysis units, and those hospitalized in nephrology departments at Cairo university hospitals, 45 cases were invited to participate in this study.

Patients were stratified according to their estimated glomerular filtration rate (eGFR) at the time of the study visit into three groups as follows: CKD stage 2 (eGFR 60 to 89 mL/min/1.73 m2) (control group), CKD stages 3 and 4 (eGFR 15 to 59 mL/min/1.73 m2), and CKD stage 5 (eGFR <15 mL/min/1.73 m2). eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[15].

This study was approved by the ethical committee of the National Research Center.

Exclusion Criteria

Non-diagnostic nocturnal polysomnography (patient did not sleep, unsatisfactory technical quality, or short monitoring time).

Treatment with Continuous positive airway pressure (CPAP).

Patients who had a tracheostomy.

Use of home oxygen therapy.

Methodology

Clinical Assessment

Full medical history, including age, sex, hypertension, congestive heart failure, coronary artery disease (angina, myocardial infarction, and coronary artery bypass surgery), cerebrovascular disease (stroke or transient ischemic attack), diabetes, pulmonary disease, and medication use. Medications included sedatives (benzodiazepines and hypnotics), antidepressants, and narcotics.

Full sleep history, including perceived sleep disturbances and sleep quality, and self-reported sleep tendency.

Thorough physical examination, including measurement of blood pressure and body mass index.

Laboratory Investigations:

Kidney function tests, including serum creatinine and serum blood urea nitrogen.

Random blood glucose level.

Complete blood count.

Polysomnography

Patients were presented to the sleep laboratory in chest department, Cairo university hospitals one hour before their usual bed time to get familiar and adapt with the environment. We provided them with full explanation of the nature and the aim of polysomnography. The duration of polysomnography monitoring was about seven continuous hours.

Patients were connected to SOMNO screen TM plus (cardio-respiratory screening) which is a computer-based high technology polysomnography (Figure 1). The study included:

Pulse oximetry applied to the index finger to detect arterial oxygen saturation (SaO_2):

Number of desaturations.

Minimal nocturnal SaO_2 (%).

Baseline saturation (%).

Average saturation (%).

Number of desaturations <90%.

Number of desaturations <80%.

Saturation time < 90%.

Average desaturation (%).

A microphone applied onto the neck beside the larynx to detect snoring.

Oronasal air flow thermal sensor and nasal pressure transducer.

Chest and abdominal movements recording using 2 separate belts to detect the effort.

Leg movements were recorded via anterior tibialis electromyogram.

From the recording of sleep study, the following data were obtained:

Total Sleep Time: Total duration of light sleep (stages N1 and N2), deep sleep (stage N3), and rapid eye movement (REM) sleep[16].

Sleep Efficiency: Total sleep time divided by the total recording time (i.e., the time in bed)[16].

Sleep Stage Latency: The duration from sleep onset to the initiation of that sleep stage[16].

Apnea

Reduction in airflow greater than ≥ 90% of baseline, recorded by oronasal thermistors or nasal pressure cannulas.

Duration ≥ 10 sec.

Reduction in airflow at least 90% of the event[17].

Classification of apneas based on respiratory effort:

Obstructive apnea: Respiratory effort is recorded throughout the event.

Central apnea: Absence of respiratory effort throughout the event.

Mixed apnea: Absence of respiratory effort at the beginning of the event followed by increasing respiratory effort during the second half[17].

Hypopnea

Reduction in airflow ≥ 50% from baseline, recorded by nasal pressure cannulas or alternatively by induction plethysmography or oronasal thermistors.

Duration ≥ 10 sec.

Reduction in airflow at least 90% of the event.

Reduction in saturation ≥ 4% from baseline prior to the event.

A desaturation is scored when these two parameters are met[17]:

Minimum drop required is 4%.

Minimum duration required is 10 seconds.

Apnea Index (AI): Number of apneas per hour of sleep[16].

Hypopnea Index (HI): Number of hypopneas per hour of sleep[16].

Apnea Hypopnea Index (AHI): Number of apneas and hypopneas per hour of sleep[16].

Respiratory Disturbance Index (RDI): Number of apneas, hypopneas, and RERAs per hour of sleep[16].

Table (1): Demographic Data Distribution of the Study Group.

Demographic Data	No.	%
Sex		
Male	27	60
Female	18	40
Age (Years)		
(Mean±SD)	(45.2±14.87)	
Smoking History		
Yes	18	40
No	27	60
Hypertension		
Yes	24	53.3
No	21	46.7
Diabetes Mellitus		
Yes	12	26.7
No	33	73.3
Cardiological Disease		
Yes	7	15.6
No	38	84.4
Cerebrovascular Disease		
Yes	1	2.2
No	44	97.8
Pulmonary Disease		
Yes	4	8.9
No	41	91.1
Drugs Use		
Yes	1	2.2
No	44	97.8
Perceived Sleep Disturbances		
Yes	27	60.0
No	18	40.0
Self-Reported Sleep Tendency		
Yes	23	51.1
No	22	48.9

Data are expressed as mean±SD for parametric data.
Data are expressed as frequency and percentage data.
45 patients were included in the study with age ranging between 15 and 70 years (Mean; 45.2±14.87).
27 out of the 45 patients were males (60%).
The prevalence of hypertension among the whole studied population was 53.3%.
27 patients (60%) gave history of perceived sleep disturbances and 23 (51.1%) had self-reported sleep tendency.

Snore Index: Number of snore events per hour of sleep.
Patient were considered to have OSA if AHI ≥ 5 events /h[16].
OSA was classified based on AHI into:
Mild OSA (AHI 5-15 events /h).
Moderate OSA (AHI 15-30/h).
Severe OSA (AHI > 30 events /h)

Statistical Analysis

Data were analyzed using statistical program for social science (SPSS) version 18.0. Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.
The following tests were done:
A one-way analysis of variance (ANOVA) when comparing between more than two means.
Chi-square (X^2) test of significance was used in order to compare proportions between two qualitative parameters.
Probability (P-value)
P-value <0.05 was considered significant.
P-value 0.01 was considered as highly significant.
P-value >0.05 was considered insignificant.

RESULTS

Using AHI for Diagnosis of Sleep Apnea

2 out of the group (I) 10 patients (20%) had sleep apnea (Mean AHI; 5.75±0.35). Both patients had mild OSA.
4 out of the group (II) 11 patients (36.4%) had sleep apnea (Mean AHI; 6±1.38). All 4 patients had mild OSA.
9 out of the group (III) 24 patients (37.5%) had sleep apnea (Mean AHI; 10.6±7.04). 7 patients (77.8%) had mild sleep apnea and 2 patients (22.2%) had moderate sleep apnea.
Overall, 15 out of the 45 studied CKD patients (33.3%) had sleep apnea (Mean AHI; 8.71±5.86). 13 patients (86.7%) had mild sleep apnea and only 2 patients (13.3%) had moderate sleep apnea.
It is evident from the above results that prevalence and severity of sleep apnea increased as eGFR declined.

Nocturnal Hypoxia

1 out of the group (I) 10 patients (10%) had nocturnal hypoxia (SaO2 below 90% for ≥12% of the nocturnal monitoring time; 13%).
3 out of the group (II) 11 patients (27.3%) had nocturnal hypoxia (Mean SaO2 below 90% for ≥12% of the nocturnal monitoring time; 13.6±1.22%).
4 out of the group (III) 24 patients (16.7%) had nocturnal hypoxia (Mean SaO2 below 90% for ≥12% of the nocturnal monitoring time; 16.75±3.30%).
Overall, 8 out of the 45 studied CKD patients (17.8%) had nocturnal hypoxia (Mean SaO2 below 90% for ≥12% of the nocturnal monitoring time; 15.1±2.87%).
It is evident from the above results that severity of nocturnal hypoxia increased as eGFR declined. Also, prevalence of nocturnal hypoxia among groups (II) and (III) were greater than group (I).

DISCUSSION

A total of 45 patients (eGFR 60 to 89 ml/min./1.73m2, n 10; eGFR 15 to 59 ml/min./1.73m2, n 11; eGFR <15 ml/min./1.73m2, n 24) were included in this study with matched mean ages across the three groups (Group (I), 45.30±9.68; Group (II), 45.27±15.82; Group (III), 45.21±16.66). No statistically significant differences between groups were found as regards age and sex **(Table 9)**.
In the present study we examined patients with the full spectrum of kidney function, ranging from those with eGFR 60 to 89 ml/min./1.73m2 to patients with eGFR <15 ml/min./1.73m2. Second, all patients were recruited from nephrology clinics and hemodialysis units, including those with minimally impaired kidney function (eGFR >60), which we believe is the most appropriate control group for this study. Third, patients were not excluded by age, sex, comorbidities, or medications, improving the generalizability of the findings to Group (II) and Group (III) CKD populations. In addition, we determined eGFR using the CKD-EPI equation, which provides a more reliable classification of patients with an eGFR

Table (2): Descriptive Data of the Study Group.

Descriptive Statistics	Min.	Max.	Mean	±SD
Body Mass Index (BMI) (kg/m2)	17.10	40.00	27.28	6.47
Systolic Blood Pressure (mmHg)	95.00	180.00	129.89	18.23
Diastolic Blood Pressure (mmHg)	60.00	110.00	82.98	11.68
Estimated Glomerular Filtration Rate (eGFR) (ml/min/1.73m2)	3.80	84.10	28.13	26.97
Creatinine (Cr) (mg/dL)	0.90	12.60	4.88	3.39
Blood Urea Nitrogen (BUN) (mg/dL)	16.00	140.00	57.51	31.81
White Blood Cell Count (WBC) (*1000/mm3)	3.40	32.70	8.78	4.95
Hemoglobin Level (Hb) (g/dL)	6.20	14.00	10.46	2.43
Platelet Count (Plt) (*1000/mm3)	88.00	620.00	217.67	107.06
Random Blood Sugar (RBS) (mg/dL)	85.00	500.00	152.93	97.78
Apnea/Hypopnea Events	1.00	67.00	14.76	17.11
Apnea/Hypopnea Index (AHI)	0.14	22.60	3.60	4.82
Oxygen Desaturation Events	1.00	60.00	12.54	17.05
Oxygen Desaturation Index	0.18	55.00	4.48	10.41
Minimal Peripheral Capillary Oxygen Saturation (SPO2) (%)	76.00	97.00	87.76	5.86
Baseline Peripheral Capillary Oxygen Saturation (SPO2) (%)	91.00	99.00	96.11	2.32
Respiratory Distress Events	1.00	203.00	53.51	51.24
Respiratory Distress Index (RDI)	0.25	44.90	12.57	10.79
Peripheral Capillary Oxygen Saturation (SPO2) Time <90%	0.10	20.00	4.69	6.63
Snore Events	1.00	3394.00	631.03	974.27
Snore Index	0.18	516.20	118.11	173.81
Sleep Efficiency (%)	8.40	91.40	69.45	19.37
Wake Events	1.00	59.00	15.63	12.24
Wake Index	0.40	12.50	3.76	3.41
Sleep Stage 1(%)	2.40	68.70	19.52	15.20
Sleep Stage 2 (%)	26.20	95.30	55.98	15.01
Sleep Stage 3(%)	0.50	37.10	12.34	8.33
Sleep Stage 4(%)	1.50	41.60	14.98	9.78
Light sleep (%)	36.40	99.50	74.52	18.00
Deep Sleep (%)	0.50	63.60	24.50	17.26

Data are expressed as mean±SD for parametric data.
The mean body mass index (BMI) (kg/m2) of the studied population was 27.28±6.47.
The mean eGFR (ml/min/1.73m2) was 28.13±26.97.
The mean AHI was 3.60±4.82.
The mean peripheral capillary oxygen saturation (SPO2) time <90% was 4.69±6.63%.

Table (3): Comparison Between Groups as Regards Sex and Age.

	Group (I) (eGFR 60 to 89 ml/min./ 1.73m2)		Group (II) (eGFR 15 to 59 ml/min./ 1.73m2)		Group (III) (eGFR <15 ml/min./ 1.73m2)		X2/F*	P-value
	No.	%	No.	%	No.	%		
Sex								
Male	5	66.67	6	54.55	16	66.67	0.997	0.607
Female	5	33.33	5	45.45	8	33.33		
Age (Years)								
Mean±SD	45.30±9.68		45.27±15.82		45.21±16.66		0.000*	1.000

Data are expressed as mean±SD for parametric data.
Data are expressed as frequency and percentage data.
* F-ANOVA test, x^2 – chi-square test; P-value >0.05 NS.
This table shows no statistically significant differences between groups as regards age and sex.
A total of 45 patients (eGFR 60 to 89 ml/min./1.73m2, n 10; eGFR 15 to 59 ml/min./1.73m2, n 11; eGFR <15 ml/min./1.73m2, n 24) were included in this study with matched mean age across the three groups (Group (I), 45.30±9.68; Group (II), 45.27±15.82; Group (III), 45.21±16.66).

>60[18].

We noticed that self-reported sleep tendency increased as eGFR declined (Group (I), 40%; Group (II), 45.5%; Group (III), 58.3%) (Table 10). This was in accordance with Roumelioti and colleagues' study which reported a higher excessive daytime sleepiness among hemodialysis patients than among control subjects (40.6% and 33%, respectively)[19].

Our Study found that mean BMI was highest among group

Table (4): Comparison Between Groups as Regards Studied Parameters.

Parameters	Group (I) (eGFR 60 to 89 ml/min./1.73m2)		Group (II) (eGFR 15 to 59 ml/min./1.73m2)		Group (III) (eGFR <15 ml/min./1.73m2)		Chi-square test	
	No.	%	No.	%	No.	%	X2	P-value
Smoking History								
Yes	5	50.0	4	36.4	9	37.5	0.540	0.763
No	5	50.0	7	63.6	15	62.5		
Hypertension								
Yes	6	60.0	5	45.5	13	54.2	0.460	0.795
No	4	40.0	6	54.5	11	45.8		
Diabetes Mellitus								
Yes	2	20.0	5	45.5	5	20.8	2.630	0.268
No	8	80.0	6	54.5	19	79.2		
Cardiological Disease								
Yes	2	20.0	2	18.2	3	12.5	0.379	0.827
No	8	80.0	9	81.8	21	87.5		
Cerebrovascular Disease								
Yes	1	10.0	0	0.0	0	0.0	3.580	0.167
No	9	90.0	11	100.0	24	100.0		
Pulmonary Disease								
Yes	2	20.0	0	0.0	2	8.3	2.607	0.272
No	8	80.0	11	100.0	22	91.7		
Drugs Use								
Yes	1	10.0	0	0.0	0	0.0	3.580	0.167
No	9	90.0	11	100.0	24	100.0		
Perceived Sleep Disturbances								
Yes	4	40.0	9	81.8	14	58.3	3.876	0.144
No	6	60.0	2	18.2	10	41.7		
Self-Reported Sleep Tendency								
Yes	4	40.0	5	45.5	14	58.3	1.136	0.567
No	6	60.0	6	54.5	10	41.7		

Data are expressed as frequency and percentage data.

P-value >0.05 NS.

This table shows no statistically significant differences between groups as regards smoking history, hypertension, diabetes mellitus, cardiological disease, pulmonary disease, drugs use, perceived sleep disturbances, or self-reported sleep tendency, using chi-square test, with p-value >0.05 NS.

Self-reported sleep tendency increased as eGFR declined (Group (I), 40%; Group (II), 45.5%; Group (III), 58.3%).

(II) patients (32.46±7.81) and lowest among the more severe group (III) patients (23.94±4.45). In consistence with our results, Alramly and colleagues found that predialysis patients with CKD had higher BMI scores than patients receiving dialysis. Loss of association between ESRD and obesity suggest that patients with ESRD are mostly exposed to loss of nutrients through dialysis treatment, anorexia, and anemia (Alramly et al., 2013). Our results revealed statistically significant differences between CKD groups as regards body mass index (BMI) **(Table 11)**.

Patients with detected sleep apnea and nocturnal hypoxia had BMI of 27.78±5.54 and 27.6±3.46, respectively. Thus, in our opinion, it is possible that altered chemical control of breathing contribute to the pathogenesis of sleep apnea in patients with CKD independently of traditional risk factors for sleep apnea such as obesity.

Our study showed that prevalence of sleep apnea increased as kidney function declined (Group (I), 20%; Group (II), 36.4%; Group (III), 37.5%). Furthermore, severity of sleep apnea increased as kidney function declined (Group (I), mean AHI: 5.75±0.35; Group (II), mean AHI: 6±1.38; Group (III), mean AHI: 10.6±7.04). Overall, 15 out of the 45 studied CKD (33.3%) patients had sleep apnea (Mean AHI; 8.71±5.86).

Beecroft and colleagues proposed several mechanisms for the increased risk of OSA among patients with CKD. First, the upper airway dimensions in patients with renal failure are prone to narrowing. They reported that the pharyngeal cross-sectional area measured by pharyngometry in end-stage renal disease patients was 12% less than that in the normal renal function control group matched for body mass index (BMI). Such pharyngeal narrowing was considered to occur because of upper airway edema due to systemic fluid overload and upper airway dilator muscle dysfunction due to neuropathy or myopathy associated with chronic uremia. Second, ventilation control is known to be instable in CKD patients. Because chemoreflex responsiveness has been reported to be augmented in patients with end-stage renal disease, possibly because of the

Table (5): Comparison Between Groups as Regards Body Mass Index and Blood Pressure.

	Group (I) (eGFR 60 to 89 ml/min./ 1.73m2))		Group (II) (eGFR 15 to 59 ml/min./ 1.73m2)		Group (III) (eGFR <15 ml/min./ 1.73m2)		ANOVA	
	Mean	±SD	Mean	±SD	Mean	±SD	F	P-value
Body Mass Index (BMI) (kg/m2)	29.60	4.22	32.46	7.81	23.94	4.45	10.572	<0.001
Systolic Blood Pressure (mmHg	126.00	13.50	137.73	20.66	127.92	18.41	1.410	0.255
Diastolic Blood Pressure (mmHg)	158.00	257.46	87.73	9.84	82.92	11.79	1.478	0.240

Data are expressed as mean±SD for parametric data.
P-value <0.001 HS; P-value >0.05 NS.
This table shows statistically significant differences between groups as regards body mass index (BMI), using ANOVA test, with p-value <0.05.
It is evident from this table that mean BMI was highest among group (II) patients (32.46±7.81) and lowest among the more severe group (III) patients (23.94±4.45).
No statistically significant differences were detected between studied groups regarding Blood Pressure.

Table (6): Comparison Between Groups as Regards Laboratory Data.

Laboratory Data	Group (I) (eGFR 60 to 89 ml/min./ 1.73m2)		Group (II) (eGFR 15 to 59 ml/min./ 1.73m2)		Group (III) (eGFR <15 ml/min./ 1.73m2)		ANOVA	
	Mean	±SD	Mean	±SD	Mean	±SD	F	P-value
Estimated Glomerular Filtration Rate (eGFR) (ml/min/1.73m2)	71.53	8.52	32.71	15.28	7.95	2.67	192.225	<0.001
Creatinine (Cr) (mg/dL)	1.09	0.12	2.52	1.09	7.55	2.26	61.065	<0.001
Blood Urea Nitrogen (BUN) (mg/dL)	17.60	1.17	46.91	22.67	79.00	21.98	36.461	<0.001
White Blood Cell Count (WBC) (*1000/mm3)	8.65	1.49	8.69	3.24	8.88	6.44	0.010	0.990
Hemoglobin Level (Hb) (g/dL)	12.80	0.75	10.65	2.51	9.40	2.18	9.706	<0.001
Platelet Count (Plt) (*1000/mm3)	229.00	73.25	183.91	42.76	229.41	137.67	0.726	0.490
Random Blood Sugar (RBS) (mg/dL)	128.00	72.39	220.00	146.07	127.21	49.49	4.146	0.024

Data are expressed as mean±SD for parametric data.
P-value <0.001 HS; P-value >0.05 NS.
This table shows statistically significant differences between groups as regards laboratory data, using ANOVA test.
It is evident from this table that hemoglobin levels decreased as eGFR declined (Group (I), 12.80±0.75; Group (II), 10.65±2.51; Group (III), 9.40±2.18).

accumulation of uremic molecules or metabolic acidosis, this destabilized respiratory control—as explained by a high "loop gain" theory—can contribute to the pathogenesis of OSA. Although these two mechanisms have been established in hemodialysis patients, it is possible that they are also applicable to the nondialysis CKD population[12].

We also found that prevalence of nocturnal hypoxia which is characteristically associated with sleep apnea was greater among groups (II) and (III) (27.3% and 16.7%, respectively) than in group (I) (10%). Severity of nocturnal hypoxia increased as kidney function declined (Group (I), 13%; Group (II), 13.6±1.22%; Group (III), 16.75±3.30%). Overall, 8 out of the 45 studied CKD patients (17.8%) had nocturnal hypoxia (Mean SaO2 below 90% for ≥12% of the nocturnal monitoring time; 15.1±2.87%). In agreement with our study, Nicholl and colleagues reported a higher prevalence of nocturnal hypoxia among patients with CKD and ESRD than in control subjects (eGFR >60 mL/min/1.73 m 2 , 16%; CKD, 47%; ESRD, 48%; P , .001).

Nocturnal hypoxia has been demonstrated to be independently associated with an increased risk for accelerated loss of kidney function (Ahmed et al., 2011). The chronic hypoxia hypothesis suggests that chronic ischemic damage in the tubulointerstitium of the kidney is the final common pathway for the development of ESRD[11]. If such a process is already under way in patients with CKD, it is possible that ongoing nocturnal hypoxia will amplify the effect and accelerate the decline in kidney function. If so, identification and treatment of nocturnal hypoxia may provide a potential disease-modifying intervention that could delay or halt the progression of CKD to ESRD.

Our study revealed that as kidney function declined, Apnea/Hypopnea (AHI) indices increased, oxygen desaturation indices increased, minimal peripheral capillary oxygen saturation values decreased, peripheral capillary

Table (7): Comparison Between Groups as Regards Sleep Studies.

Sleep Studies	Group (I) (eGFR 60 to 89 ml/min./1.73m2)		Group (II) (eGFR 15 to 59 ml/min./1.73m2)		Group (III) (eGFR <15 ml/min./1.73m2)		ANOVA	
	Mean	±SD	Mean	±SD	Mean	±SD	F	P-value
Apnea/Hypopnea Events	4.78	6.70	14.09	14.85	18.81	19.48	2.352	0.108
Apnea/Hypopnea Index (AHI)	1.03	1.72	3.42	2.44	4.64	6.01	1.926	0.159
Oxygen Desaturation Events	2.00	1.22	23.14	22.81	11.19	14.95	2.646	0.091
Oxygen Desaturation Index	0.39	0.34	4.21	4.30	5.88	3.42	0.513	0.605
Minimal Peripheral Capillary Oxygen Saturation (SPO2) (%)	91.20	2.57	88.09	4.74	86.17	6.75	2.846	0.069
Baseline Peripheral Capillary Oxygen Saturation (SPO2) (%)	96.30	1.06	95.55	2.91	96.29	2.44	0.422	0.658
Respiratory Distress Events	14.50	22.97	51.73	32.80	67.33	58.62	3.593	0.037
Respiratory Distress Index (RDI)	3.06	5.87	14.87	4.78	14.68	12.40	4.437	0.018
Peripheral Capillary Oxygen Saturation (SPO2) Time <90%	1.45	3.46	4.63	6.75	6.90	7.63	1.704	0.202
Snore Events	.	.	78.50	147.83	841.52	1073.58	3.924	0.048
Snore Index	.	.	26.05	49.69	153.18	191.69	3.361	0.037

Data are expressed as mean±SD for parametric data.

P-value <0.05 S; P-value >0.05 NS.

This table shows statistically significant differences between groups as regards respiratory distress events, respiratory distress index (RDI), snore events, and snore index.

Apnea/Hypopnea (AHI) Indices increased as eGFR declined (Group (I), 1.03±1.72; Group (II), 3.42±2.44; Group (III), 4.64±6.01).

Oxygen desaturation indices increased as eGFR declined (Group (I), 0.39±0.34; Group (II), 4.21±4.30; Group (III), 5.88±13.42).

Minimal peripheral capillary oxygen saturation values decreased as eGFR declined (Group (I), 91.20±2.57; Group (II), 88.09±4.74; Group (III), 86.17±6.75).

Respiratory distress index (RDI) was lowest among group (I) (3.06±5.87) and higher among groups (II) and (III). Respiratory distress indices (RDI) among groups (II) and (III) were very similar (14.87±4.78 and 14.68±12.40).

Peripheral capillary oxygen saturation time <90% increased as eGFR declined (Group (I), 1.45±3.46; Group (II), 4.63±6.75; Group (III), 6.90±7.63).

Snore index was higher among group (III) patients (153.18±191.69) than in group (II) patients (26.05±49.69).

oxygen saturation time <90% increased, and snore indices increased (Table 13). Also, respiratory distress index (RDI) was higher among groups (II) and (III) than in group (I) (Table 13). However, only differences between groups as regards respiratory distress events, respiratory distress indices, snore events, and snore indices were statistically significant. These results show that as kidney function declines, several respiratory parameters deteriorate during sleep.

In addition, wake events and indices, and sleep stage 1 (%) increased as kidney function deteriorated (Table 14). Sleep efficiency (%) was highest among group (I) patients and lower among groups (II) and (III), Light sleep (%) was lowest among group (I) patients and higher among groups (II) and (III), and deep sleep (%) was highest among group (I) patients and lower among groups (II) and (III) (Table 14). It is clear from the above results that as kidney function declines, sleep efficiency deteriorates, wake indices increase, light sleep (%) increases, and deep sleep (%) decreases.

Previous studies have evaluated the prevalence of sleep apnea in CKD. Markou and colleagues[21] reported a 31.4% prevalence of sleep apnea in a cross-sectional study of 35 patients with CKD, which is similar to our overall 33.3% prevalence.

Sim and colleagues[22] reported an increased risk for sleep apnea in CKD patients with eGFR <90 mL/min per 1.73 m2, excluding those with eGFR <15 mL/min per 1.73 m2 and end stage renal disease (ESRD) patients, thus limiting the generalizability of their study. They found a 2.5% prevalence of sleep apnea among their patients. They used the International Classification of Diseases, ninth revision, coding for SA and Current Procedural Terminology coding for positive airway pressure devices. Kidney function was assessed by the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation, and logistic regression was used to estimate the relative risk for SA. Dias et al.'s study showed that the new CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation appears to reflect GFR results more

Table (8): Comparison Between Groups as Regards Sleep Studies.

Sleep Studies	Group (I) (eGFR 60 to 89 ml/min./ 1.73m2)		Group (II) (eGFR 15 to 59 ml/min./ 1.73m2)		Group (III) (eGFR <15 ml/min./ 1.73m2)		ANOVA	
	Mean	±SD	Mean	±SD	Mean	±SD	F	P-value
Sleep Efficiency (%)	75.78	9.96	66.96	19.73	68.22	21.85	0.608	0.549
Wake Events	10.00	7.12	12.09	9.04	19.59	13.97	3.031	0.039
Wake Index	1.81	1.29	4.19	3.52	4.38	3.75	2.249	0.118
Sleep Stage 1(%)	8.60	6.31	20.81	14.85	23.48	16.18	3.884	0.028
Sleep Stage 2 (%)	59.70	5.29	57.11	18.32	53.92	16.23	0.552	0.580
Sleep Stage 3(%)	14.95	4.87	10.00	6.81	12.32	9.88	0.923	0.405
Sleep Stage 4(%)	17.15	7.09	18.96	15.03	12.06	8.07	1.646	0.209
Light Sleep (%)	67.90	10.30	77.92	21.22	75.73	18.88	0.923	0.405
Deep Sleep (%)	31.70	10.30	22.08	21.22	22.60	17.43	1.129	0.333

Data are expressed as mean±SD for parametric data.

P-value <0.05 S; P-value >0.05 NS.

This table shows statistically significant differences between groups as regards wake events and sleep stage 1 (%).

Sleep efficiency (%) was highest among group (I) patients (75.78±9.96) and lower among groups (II) and (III). Sleep efficiency (%) among groups (II) and (III) were very similar (66.96±19.73 and 68.22±21.85).

Wake indices increased as eGFR declined (Group (I), 1.81±1.29; Group (II), 4.19±3.52; Group (III), 4.38±3.75).

Sleep stage 1 (%) increased as eGFR declined (Group (I), 8.60±6.31; Group (II), 20.81±14.85; Group (III), 23.48±16.18).

Light sleep (%) was lowest among group (I) patients (67.90±10.30) and higher among groups (II) and (III). Light Sleep (%) among groups (II) and (III) were very similar (77.92±21.22 and 75.73±18.88).

Deep sleep (%) was highest among group (I) patients (31.70±10.30) and lower among groups (II) and (III). Deep sleep (%) among groups (II) and (III) were very similar (22.08±21.22 and 22.60±17.43).

accurately than MDRD, and thus should be the method of choice for estimating GFR.

Sagakuchi and colleagues[23] found that Japanese individuals with CKD had a high prevalence (65%) of AHI ≥5 events/h, with one-third of the cohort classified as having moderate (AHI 15 to 29 events/h) or severe (AHI ≥30 events/h) OSA. They used a different modified equation to calculate eGFR for their patients as follows: eGFR = 194 × sCr−1.094 × age−0.287 × 0.739 (if female). In contrast to our study, their work excluded the following: (1) patients who had already undergone renal replacement therapy, (2) those who presented with acute renal failure, and (3) those with severe acute complications such as acute coronary syndrome, acute heart failure, stroke, and systemic infection. The diagnosis of OSA and its severity in their study were measured using a type 3 portable monitor (Morpheus, Teijin Pharma Ltd., Japan).

Roumelioti and colleagues[19] reported that OSA is common among individuals with severe CKD (mean eGFR 18.9 ± 7.6 ml/min per 1.73 m2) and those on dialysis therapy compared with a community-based cohort (eGFR 91.8 ± 19.2 ml/min per 1.73 m2). The dialysis group had significantly greater stage 1 ("light sleep") and significantly less stage 2 sleep. Both CKD and hemodialysis groups were more likely to have severe OSA and nocturnal hypoxemia. In agreement with Roumelioti et al., our study revealed increased prevalence and severity of OSA as eGFR declined. Also, in our study, CKD patients with eGFR <15 ml/min./1.73m2 had significantly greater sleep stage 1 ("light sleep") than the other CKD groups and statistically insignificant less sleep stage 2. We found that CKD patients with eGFR <60 mL/min/1.73 m2 had greater light sleep % and less deep sleep % in comparison with the control group (eGFR 60 to 89 ml/min./1.73m2) (Table 14).

Nicholl and colleagues found that the prevalence of sleep apnea increased as eGFR declined (eGFR greater or equal to 60 mL/min/1.73 m2, 27%; CKD, 41%; ESRD, 57%; P 5 .002). Their results matches well with ours (Group (I), 20%; Group (II), 36.4%; Group (III), 37.5%).

Fleischmann and colleagues[24] examined 158 patients with CKD who were already suspected of having sleep apnea and, using PSG as an objective measure, were able to document very high rates of sleep apnea (80%-94%). These workers defined sleep apnea differently as the respiratory disturbance index (RDI) > 5 . In this context, Goetting and colleagues claim that the use of the standard method AHI alone for diagnosing OSA leads to underdiagnosis in 30% of cases as compared to the use of the RDI[25]

CONCLUSION AND RECOMMENDATIONS

Prevalence and severity of sleep apnea in patients with CKD increase as kidney function declines.

Almost 18% of patients with CKD experience nocturnal hypoxia that becomes more common and severe as kidney function declines, which may contribute to loss of kidney function.

Further studies are required to determine whether treatment of sleep apnea and nocturnal hypoxia improves this clinical outcome in patients with CKD.

ACKNOWLEDGMENT

Before all, Thanks to **GOD**.

I wish to express my deepest gratitude and respect to Prof. Ahmed Abd-El-Meguid El-Hadidy, Professor and Head of Chest Diseases Department, Faculty of Medicine, Cairo University for his kind supervision of this work, objective criticism, continous support and meticulous guidance.

I am also much obliged to Professor. Nada Ezz-El-Din Gomaa, Professor of Chest Diseases, National Research Center for her valuble support, guidance and encouragement.

I would like to express my gratitude to Prof. Tarek Hussein El-Shabouny, Professor of Nephrology, Faculty of Medicine, Cairo University for his fruitful criticism, continuous and valuable encouragement.
I am very thankful to Dr. Youssef Mohamed Amin, Assistant Professor of Chest Diseases, Faculty of Medicine, Cairo University, who spent much time and effort guiding and supporting me throughout this study.
My thanks and recognition to Dr. Eman Kamal, Lecturer of Chest Diseases, Cairo University who guided and helped me in carrying out polysomnography to the patients included in this study.

REFERENCES

1. Ahmed SB, Ronksley PE, Hemmelgarn BR, et al. Nocturnal hypoxia and loss of kidney function. PLoS ONE. 2011; 6(4): e19029.
2. Beecroft J, Duffin J, Pierratos A, Chan CT, McFarlane P, Hanly PJ: Enhanced chemo-responsiveness in patients with sleep apnoea end end-stage renal disease. Eur Respir J 28: 151–158, 2006.
3. Beecroft JM, Hoffstein V, Pierratos A, Chan CT, McFarlane PA, Hanly PJ: Pharyngeal narrowing in end-stage renal disease: Implications for obstructive sleep apnea. Eur Respir J 30: 965–971, 2007.
4. Berry RB1, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, Marcus CL, Mehra R, Parthasarathy S, Quan SF, Redline S, Strohl KP, Davidson Ward SL, Tangredi MM. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med. 2012; 15;8(5):597-619.
5. De Backer WA. Central sleep apnoea, pathogenesis and treatment: an overview and perspective. [Review] [119 refs]. Eur Respir J 1995; 8: 1372–1383.
6. Elwood P, Hack M, Pickering J, Hughes J, Gallacher J. Sleep disturbance, stroke, and heart disease events: evidence from the Caerphilly cohort. J Epidemiol Community Health 2006; 60: 69–73.
7. Engleman HM, Douglas NJ. Sleep. 4: Sleepiness, cognitive function, and quality of life in obstructive sleep apnoea/hypopnoea syndrome. Thorax 2004; 59: 618–622.
8. Fine LG, Norman JT. Chronic hypoxia as a mechanism of progression of chronic kidney diseases: from hypothesis to novel therapeutics. Kidney Int. 2008; 74 (7): 867 - 872.
9. Fleischmann G, Fillafer G, Matterer H, Skrabal F, Kotanko P. Prevalence of chronic kidney disease in patients with suspected sleep apnoea. Nephrol Dial Transplant. 2010; 25:181–186.
10. Fletcher EC. Obstructive sleep apnea and the kidney. J Am Soc Nephrol. 1993; 4 (5): 1111 - 1121.
11. Goetting, C, Downey III R. Sick, symptomatic and undiagnosed. San Antonio, TX: 2010.
12. Heslegrave R, Thornley K, Ouwendyk M. Impact of nocturnal hemodialysis on sleep and daytime cognitive functioning in patients with chronic renal failure [abstract]. Sleep. 1998; 21: 51.
13. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A New Equation to Estimate Glomerular Filtration Rate. Ann Intern Med 150(9): 604-12. (2009)
14. Markou N, Kanakaki M, Myrianthefs P, et al. Sleepdisordered breathing in nondialyzed patients with chronic renal failure. Lung. 2006; 184:43–49.
15. Redline S, Yenokyan G, Gottlieb DJ, et al. Obstructive sleep apnea-hypopnea and incident stroke: the Sleep Heart Health study. Am J Respir Crit Care Med. 2010; 182 (2): 269-277.
16. Roumelioti, et al.: Clin J Am Soc Nephrol 6: 000–000, 2011.
17. Sakaguchi Y, Shoji T, Kawabata H, Niihata K, Suzuki A, Kaneko T, Okada N, Isaka Y, Rakugi H, Tsubakihara Y: High prevalence of obstructive sleep apnea and its association with renal function among non-dialysis chronic kidney disease patients in Japan: A cross-sectional study. Clin J Am Soc Nephrol 6: 000–000, 2011.
18. Sim JJ, Rasgon SA, Kujubu DA, Kumar VA, Liu IL, Shi JM, Pham TT, Derose SF: Sleep apnea in early and advanced chronic kidney disease: Kaiser Permanente Southern California cohort. Chest 135: 710–716, 2009.
19. Stevens LA , Schmid CH , Greene T , et al . Comparative performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study equations for estimating GFR levels above 60 mL/min/1.73 m 2 . Am J Kidney Dis . 2010; 56 (3): 486 - 495.
20. Stradling JR, Davies RJ. Sleep. 1: Obstructive sleep apnoea/hypopnoea syndrome: definitions, epidemiology, and natural history. Thorax 2004; 59: 73–78.
21. Tsara V, Amfilochiou A, Papagrigorakis MJ, Georgopoulos D, Liolios E Alexopoulou C, Maniou C, Kithreotis P, Trakada G, Synodinos F, Vilos G, Steiropoulos P. Guidelines for Diagnosing and Treating Sleep related Breathing Disorders in Adults and Children. HIIPPOKRATIIA 2009, 13(4): 2647-26562.
22. Zoccali C, Mallamaci F, Tripepi G. Traditional and emerging cardiovascular risk factors in end-stage renal disease. Kidney Int Suppl. 2003; (85): S105 - S110.
23. Zoccali C, Mallamaci F, Tripepi G, Benedetto FA. Autonomic neuropathy is linked to nocturnal hypoxaemia and to concentric hypertrophy and remodelling in dialysis patients. Nephrol Dial Transplant 2001; 16: 70–77.